UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,146	09/16/2002	Wilhelm Amberg	51748	9829

32116 7590 02/28/2005

WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
500 W. MADISON STREET
SUITE 3800
CHICAGO, IL 60661

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,146	AMBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 are pending.

2. Applicant's election without traverse of Group II, claims 4-6 and 10 drawn to a pharmaceutical composition comprising an endothelin blocker and an αvβ3 integrin receptor antagonist and a trade package filed on 12/27/04, is acknowledged.

3. Claims 1-3 and 7-9 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 4-6 and 10 are under examination as they read on a pharmaceutical composition comprising an endothelin blocker and an αvβ3 integrin receptor antagonist and a trade package.

5. References N-Q and U-W cited on the PTO FORM 892 is issued from the references cited in the Search Report of PCT/EP00/0971 and will not be supplied. Reference DE 198 09 144 A was not considered and hence not listed on the PTO FORM 892 because the English translation of the reference was not found. Applicant is invited to provide the English translation of said reference.

6. The specification is objected to because of the following informalities:

A. The term "myokard infarkt" on page 4, line 39, is not an English term.

B. The word "Pohosphoramidon" on page 5, line 40, is misspelled. The correct spelling is "phosphoramidon".

C. The term "CGS-35066" disclosed on page 5, line 45 is a duplication of the same term on page 6, line 1.

D. The "SD-187" with its chemical name on page 11, lines 12-19, is the same as (2S)-2-{[(4-isobutylphenyl) sulfonyl]amino}-3-.... propanoic acid) disclosed on page 11, lines 5-10.

7. Claims 4 and 10 are objected to under 37 CFR 1.75(i), as being improper because they fail to indent each element of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4-6 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. It is improper to recite "Pharmaceutical composition" in claim 4. It is suggested that article "A" be inserted before "Pharmaceutical composition".

B. It is improper to recite "composition" in claims 5 and 6. It is suggested that word "The" be inserted before "composition".

C. It is improper to recite "Trade package" in claims 5 and 6. It is suggested that word "A" be inserted before "Trade package".

D. The "composition" recited in claim 5 has no antecedent basis in base claim 4. Base claim 4 only recites pharmaceutical composition.

10. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

11. Claim 6 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

The instant application has provided a description of endothelin blockers and αvβ3 integrin receptor antagonists. The specification discloses that both receptors, namely ET receptors and integrin αvβ3, play a role in restenosis after vascular injury both in animal models and in man (see page 4, lines 4-6). Further, the specification asserts that by inhibiting either of the two principles, a 30% to 40% reduction of neointima formation (the leading cause of restenosis, (see page 2, line 43)) could be achieved in the relevant experimental models (see page 4, lines 6-8). The specification asserts that by combining compounds which act as ET blockers and αvβ3 integrin receptor antagonist in one formulation or as a kit, it is possible to achieve a reduction of restenosis significantly more pronounced than applying one of the two treatments alone at the given doses (see page 4, line18-23). Further, the specification discloses that endothelin blocker in combination with αvβ3 integrin receptor antagonist can be used for the manufacture of medicaments for the treatment or prevention of diseases, particularly of cardiovascular disorders, particularly of restenosis after vessel injury or revascularisation treatment (see page 4, lines 29-34). The instant specification asserts that the specific cardiovascular disorders are atherosclerosis, restenosis after vessel injury or revascularisation treatment, angioplasty (neointima formation, smooth muscle cell migration and proliferation), myocardial infaraction or heart failure (on page 4, lines 36-39). The specification further discloses alternate administration techniques and dosages that are specific and conventional techniques for drug administration (see pages 13-14). Claim 6 recites curing cardiovascular disorders. The specification fails to provide working examples that demonstrate the specifically asserted utility of curing cardiovascular disorders.

The specification asserts a specific utility of curing cardiovascular disorder for the claimed composition comprising an endothelin blocker and an αvβ3 integrin receptor antagonist. A cure for cardiovascular disorders is a desirable outcome based upon a need in the art. Therefore, the disclosed use of the claimed composition is specific, substantial and "real world". However, one skilled in the art knows that the cardiovascular disorders have no known cure. For Example, a publication regarding cardiovascular diseases (Cleveland Clinic Health Information center), provides a teaching that for those patients still at risk of a heart attach or stroke despite lifestyle changes and medication use, or for those who have sever arterial blockage, interpreventional procedures or surgery is often recommended. However, these procedures do not cure cardiovascular disease, so lifestyle changes such as a healthy diet, exercising regularly and quitting smoking continue to play major roles in having a healthy heart (see page 6, under Interventional procedures and surgery in particular). The specification does not contain evidence for the use of the claimed composition in curing all and every cardiovascular disorders. While the specification asserts that the use of the claimed composition can achieve a reduction of restenosis, the specification fails to provide evidence that a claimed treatment will effect a cure. Therefore, it would be reasonable to conclude that the utility would not be credible based on the evidence of record.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 6 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

14. Further, claims 4-5 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition or a trade package, comprising as pharmaceutical agent, ET_A endothelin blocker and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agent for the treatment of restenosis after vessel injury or a cardiovascular disorder that involve ET_A receptor and αvβ3 integrin antagonist, does not reasonably provide enablement a pharmaceutical composition comprising any "endothelin blocker" and an αvβ3 integrin receptor antagonist in claim 4, or a trade package comprising as pharmaceutical agent an "endothelin blocker" and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agent for the treatment or "prevention" of any "disease" in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Claim 4 recites a composition comprising any endothelin blocker and an αvβ3 integrin receptor antagonist. The specification on page 2, line 11-25, discloses that endothelin (ET) binds in an autocrine/paracrine fashion to two different specific high affinity receptors, named ET_A and ET_B. The specification further discloses that ET_A receptors are only located on smooth muscle cells leading to vasoconstriction and SMC proliferation. Further, a variable portion of ET_B receptors were also described on SMCs promoting at that location the same effect as ET_A receptors via the same intracellular signaling pathways. The specification on page 2, line 27 discloses that it is known that ET_A receptor antagonists effect restenosis. However, Munter *et al* teach that the agents developed thus far inhibit the actions of ET through either selective inhibition of the ET_A receptors or non-selective inhibition of both ET_A and ET_B receptors. Munter *et al* also teach that binding of ET-1 to ET_A and ET_B receptors will result mostly in opposing effects, as vasoconstriction and mitogenesis are primarily mediated via ET_A receptors and vasodilatation exclusively via ET_B receptors. Further, during blockade of ET_B receptors, endogenous ET levels are increased and the ET_B receptor serves as a clearance receptor. Munter *et al* teach that selective ET_B receptor blockade has never seriously been considered as therapeutic option (see page 4, under section 2.1). Thus, ET_A antagonist and ET_B antagonist are mutually exclusive in that they reach opposing endpoints. Therefore, the use of ET_B antagonists as a therapeutic agent is unpredictable.

Further, at issue is whether or not the claimed composition or trade package comprising as a pharmaceutical agent: an endothelin blocker and an αvβ3 integrin receptor antagonist would function "for the treatment or prevention of diseases" including cardiovascular disorders i.e., whether or not the claimed trade package or composition would function to treat and prevent any and every disease. The specification discloses the ET receptors and integrin αvβ3 play a role in restenosis after vascular injury both in animal and in man (see page 4, lines 4-6). The specification lacks examples on how to treat or prevent any disease including cardiovascular disorders. Further, the specification fails to provide guidance as to how to treat or prevent any pathological condition of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress. Besides, the treatment of the cardiovascular disorders that involve both the ET_A receptor (located on the smooth muscle) and the αvβ3 receptor, and the prevention of said cardiovascular disorders subsequent to a surgery or injury. The specification does not disclose how to treat/prevent cardiac muscle diseases. Further, the specification fails to provide guidance on how to treat/prevent any disease for example: Duchenne muscular disorder, myotonic dystrophy or mitochondrial myopathies, wherein skeletal muscle is involved in the disease, or diseases such as psoriasis, or allergy using the claimed composition of the invention. Thus in the absence of working examples or detailed guidance in the specification, the intended uses of any pharmaceutical composition comprising an endothelin blocker and an αvβ3 integrin receptor antagonist are fraught with uncertainties.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the

nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* (provided in the International Report and cited on the PTO-892 as reference Y) in view of Srivatsa *et al* (provided in the International Report and cited on the PTO-892 as reference W).

Kirchengast *et al* teach 8 endothelin blockers such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 that were tested in different models of restenosis (a cardiovascular disorder) in rats and pigs. Kirchengast *et al* also teach that both the selective ET_A receptor antagonist FR 139317 and the mixed $ET_{A/B}$ receptor antagonist TAK 044 were able to reduce neointima proliferation by 76% and 80%, respectively. Further, the balanced $ET_{A/B}$ receptor antagonist SB 209670 was shown to reduce the neointima/media ration by 52%. Furthermore, BMS 182874 and LU135252 were able to reduce neointima/media ration by 35% and 25%, respectively (see page 552 under Endothelin antagonism in experimental restenosis and table 1 in particular).

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition, comprising an endothelin blocker and an $\alpha v\beta 3$ integrin receptor antagonist in claim 4.

However, Srivatsa *et al* teach that selective $\alpha v\beta 3$ integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury (a cardiovascular disorder). Srivatsa *et al* also tested the effect of the XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic $\alpha v\beta 3$ antagonist on neointimal hyperplasia and lumen stenosis in a porcine

coronary injury model (see age 424, 2nd col., at the end of the 2nd paragraph in particular). Srivatsa *et al* concluded that in large animal coronary stent restenosis model, use of a selective high affinity αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia and lumen stenosis (see page 426, last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the endothelin blockers taught by Kirchegast *et al*, with the selective αvβ3 integrin antagonist XJ 735 taught by Srivatsa *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the endothelin blockers are able to reduce neointima proliferation (i.e., restenosis) as taught by Kirchengast *et al* and because the αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia the leading cause of restenosis. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* (provided in the International Report and cited on the PTO-892 as reference Y) in view of Srivatsa *et al* (provided in the International Report and cited on the PTO-892 as reference W) as applied to claims 4-6 above, and further in view of US Pat. No. 4,761,406.

The teachings of Kirchengast *et al* and Srivatsa *et al* have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a trade package (kit) comprising as pharmaceutical agent, an endothelin blocker and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agents in claim 10.

The `406 patent teaches kits which facilitate the necessary strict compliance with methods of treatments (e.g., see col., 1, lines 9-12; col., 2, lines 24-26, and columns 13-15 in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the endothelin blocker such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 taught by Kirchengast *et al* and αvβ3 integrin receptor antagonist such as XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic taught by Srivatsa *et al* in a kit to facilitate the necessary strict compliance with methods of treatments

One would have been motivated to assemble the endothelin blocker and the αvβ3 integrin receptor antagonist in a kit format for conveniently and effectively implementing the method of treatment as taught by the `406 patent.

It is noted the only active ingredient in the claimed trade package (kit) is the endothelin blocker and the αvβ3 integrin receptor antagonist. Although the kits comprise instructions, there is no patentable weight given to the instructions themselves. It would have been prima facie obvious to the ordinary artisan to include a piece of paper in the kit identifying the components therein at the time the invention was made.

It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Also, see In re Haller 73 USPQ 403 (CCPA 1947), where application of printed matter to old article cannot render article patentable and In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 22, 2005

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600